Intensive Blood Pressure Lowering in Patients With and Patients Without Type 2 Diabetes: A Pooled Analysis From Two Randomized Trials

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OBJECTIVE

The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP) study did not find a significant beneficial effect of intensive systolic blood pressure (SBP) lowering on cardiovascular events in hypertensive patients with type 2 diabetes mellitus (T2DM), while the Systolic Blood Pressure Intervention Trial (SPRINT) did find a significant beneficial effect in patients without T2DM. The objective of this analysis was to assess the effect of both T2DM and baseline cardiovascular disease risk on the treatment effect of intensive blood pressure lowering.

RESEARCH DESIGN AND METHODS

The individual patient data from the ACCORD-BP and SPRINT studies were pooled and follow-up durations harmonized. Both studies randomized hypertensive patients to an SBP target of <120 mmHg or a target of <140 mmHg. The composite primary end point consisted of unstable angina, myocardial infarction, acute heart failure, stroke, and cardiovascular death. The interaction between intensive blood pressure lowering and both T2DM and 10-year cardiovascular risk was assessed using Cox proportional hazards models.

RESULTS

The cohort consisted of 14,094 patients with mean age 66 ± 8.9 years and mean baseline SBP 139.5 ± 15.6 mmHg; 33.6% had T2DM. The hazard ratio for the primary composite end point was 0.82 (95% CI 0.73–0.93), *P* = 0.0017. The interaction between intensive blood pressure lowering and T2DM was nonsignificant (*P* = 0.13). The 10-year cardiovascular risk was higher in primary prevention patients with T2DM, but risk did not interact with the treatment effect (*P* = 0.84).

CONCLUSIONS

Intensive blood pressure lowering may have a similar favorable effect and appears to decrease cardiovascular events in both patients with and patients without T2DM.

Hypertension and type 2 diabetes mellitus (T2DM) are both highly prevalent in the Western world and increase the risk of cardiovascular disease (CVD) (1–3). The benefit of a systolic blood pressure (SBP) target of <120 mmHg vs. <140 mmHg on the reduction of cardiovascular events was assessed in two large randomized clinical trials (4,5). The Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD-BP)

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trial and the Systolic Blood Pressure Intervention Trial (SPRINT) assessed the effect in persons with T2DM at high risk (ACCORD-BP) and in persons without T2DM at high risk (SPRINT).

ACCORD-BP did not demonstrate a statistically significant benefit of intensive blood pressure lowering on the primary composite end point, while SPRINT did. The current guidelines recommend an SBP target of <140 mmHg in patients with T2DM based on ACCORD-BP, while the results of SPRINT have not been incorporated in the guidelines (6–9).

The difference in outcomes in ACCORD-BP and SPRINT have been attributed to differences in study design, sample size, interaction between T2DM and the intervention, or play of chance (5). Furthermore, the primary composite end point of SPRINT consisted of two additional components, unstable angina and acute cardiac decompensation, compared with ACCORD-BP (myocardial infarction, stroke, and cardiovascular death). This increased the event rate and possibly the treatment effect of intensive blood pressure lowering in SPRINT.

The objectives of this study were as follows: *1*) to evaluate the treatment effect of intensive blood pressure lowering in patients with T2DM and patients without T2DM using the individual patient data of ACCORD-BP and SPRINT and using the same composite primary end points and follow-up durations and *2*) to assess the interaction between both T2DM and baseline CVD risk and the treatment effect of intensive blood pressure lowering, as patients with T2DM have a higher 10-year risk of CVD than patients without T2DM.

RESEARCH DESIGN AND METHODS

Study Design and Intervention

The design, rationale, and outcomes of ACCORD-BP and SPRINT have previously been described including detailed inclusion and exclusion criteria (4,5,10,11) (online study protocols: https://biolincc.nhlbi.nih.gov/studies/accord/ and https://biolincc.nhlbi.nih.gov/studies/sprint_pop/). In brief, both studies were randomized, open-label multicenter trials that assigned participants at high risk of cardiovascular events with an SBP between 130 mmHg and 180 mmHg to an SBP target of either <120 mmHg (the intensive treatment group) or <140 mmHg (the standard treatment group). Action to Control Cardiovascular Risk in Diabetes (ACCORD) enrolled 10,251 participants with T2DM in a 2-by-2 factorial design in the U.S. and Canada between the years 2001 and 2005. All participants were randomly assigned to either intensive or standard glycemic control. Additionally, a subgroup of 4,733 participants were also randomly assigned to either intensive or standard blood pressure control: the ACCORD-BP trial, which was used for this analysis. SPRINT randomized patients directly to intensive or standard blood pressure lowering and recruited patients in the U.S. between 2010 and 2013. Blood pressure and pulse were measured three times after 5 min of seated rest at each clinic visit in both trials with an automated device (Model 907; Omron Healthcare, Lake Forest, IL) and averaged. ACCORD was designed to have 94% power to detect a 20% reduction in the rate of the primary outcome in the intervention arm and SPRINT to have 89% power. Both studies were sponsored by the U.S. National Heart, Lung, and Blood Institute and approved by the institutional review boards of the participating study sites. The use of both data sets was approved by the institutional review board of the Academic Medical Center, Amsterdam, the Netherlands.

Population

Participants were eligible for ACCORD-BP if they were diagnosed with T2DM, had a glycated hemoglobin level ≥7.5%, and were ≥40 years of age with a history of CVD or ≥55 years of age with anatomical evidence of a substantial amount of atherosclerosis, albuminuria, left ventricular hypertrophy, or at least two additional risk factors for CVD (dyslipidemia, hypertension, smoking, or obesity). Participants were also required to have an SBP between 130 mmHg and 180 mmHg while taking three or fewer antihypertensive medications.

Eligible SPRINT participants were required to be ≥50 years old, without T2DM, and to have an SBP between 130 mmHg and 180 mmHg and an increased risk of cardiovascular events, defined as clinical or subclinical CVD other than stroke, chronic kidney disease with an estimated glomerular filtration rate between 20 and 60 mL/min/1.73 m^2 body surface area, a 10-year risk of CVD ≥15% on the basis of the Framingham risk score, or age ≥75 years.

Main Outcomes of the Original Studies

The ACCORD-BP composite primary end point consisted of myocardial infarction, stroke, and cardiovascular death. The SPRINT composite primary end point consisted of the same end points plus acute coronary syndrome not resulting in myocardial infarction and acute decompensated heart failure. After a mean follow-up of 5 years, the hazard ratio for the occurrence of cardiovascular events in ACCORD-BP was 0.88 (95% CI 0.73–1.06), nonsignificantly in favor of intensive blood pressure control. SPRINT enrolled 9,361 participants without T2DM in the U.S. After a mean follow-up of 3.26 years, the study was terminated early owing to the significantly lower event rate in the intensive treatment arm. The hazard ratio for the occurrence of cardiovascular events was 0.75 (95% CI 0.64–0.89), significantly in favor of intensive blood pressure control. The secondary outcomes acute heart failure, cardiovascular mortality, and all-cause mortality were also significantly reduced. A committee blinded to treatment assignment adjudicated the clinical outcomes in each study.

Pooled Cohort

The data of ACCORD-BP and SPRINT were merged. In the ACCORD-BP subset, the SPRINT composite end point was constructed by combining the ACCORD-BP primary end point (myocardial infarction, stroke, and cardiovascular death) with unstable angina and acute decompensated heart failure events. Additionally, the follow-up duration was truncated in ACCORD-BP to the median follow-up duration of SPRINT: 3.26 years (Supplementary Figs. 1 and 2). The 10-year risk score of CVD was calculated in the subset of patients without a history of cardiovascular events (12). The safety end point from the original studies was used and consisted of serious adverse events related to blood pressure–lowering therapy.

Statistical Analysis

For the analysis, patients enrolled in ACCORD-BP were considered to have T2DM and those enrolled in SPRINT were not considered to have T2DM. Baseline characteristics were compared using Student *t* test, Mann-Whitney *U* test, or

Fisher exact test when appropriate. Time-to-event analysis of the composite primary and secondary end points in the two treatment groups was performed with Cox proportional hazards regression. The status of T2DM (yes vs. no) was added to the Cox model, and subsequently an interaction term between T2DM and treatment allocation was added. The model fit with and without the interaction term was compared using Akaike information criterion (AIC) and ANOVA. The same was done for the baseline 10-year risk score of CVD grouped per 20% increments in patients without a history of CVD. Post hoc power calculations were performed using the SPRINT composite end point and a median follow-up of 3.26 years. For serious adverse events related to blood pressure–lowering therapy, the proportions were calculated using the crude numbers from the main outcomes paper, as these data were not part of the public ACCORD data set. *P* values <0.05 were considered statistically significant. All statistical analyses were conducted in R Studio and R version 3.3.1 (13).

RESULTS

Baseline of the Pooled Cohort

The pooled cohort of ACCORD-BP and SPRINT consisted of 14,094 patients (Supplementary Fig. 3). Table 1 shows baseline characteristics of participants per study and per treatment allocation. At baseline, the two studies differed significantly except for baseline SBP, smoking, and aspirin use. The distribution of 10-year risk score of CVD was different in the two studies (Supplementary Fig. 4). Patients in the pooled cohort had a mean age of 66 $\pm$ 8.9 years, and 39.7% were female.

The randomization remained intact when the baseline characteristics were judged both by absolute numbers and statistically. The mean SBP at baseline was 139.5 $\pm$ 15.6 mmHg and the mean diastolic blood pressure was 77.4 $\pm$ 11.5 mmHg. In the pooled cohort, 33.6% of patients had T2DM and the median 10-year risk of CVD was 25% (quartiles 17, 26).

Primary and Secondary Outcomes

The incidence of the primary end point in the pooled cohort was 7.3% during a median follow-up of 3.26 years. The event rate was 8.0% in the intensive treatment group vs. 6.6% in the standard treatment group. The hazard ratio for the primary composite end point was 0.82 (95% CI 0.73–0.93), $P = 0.002$ (Fig. 1). The individual secondary end points were not significantly different between the treatment groups, except acute heart failure events (Fig. 2). Cardiovascular mortality and all-cause mortality were nonsignificantly lower. The post hoc calculated power in the pooled cohort for the primary composite end point was 88.9%.

T2DM

The event rate in patients with T2DM was higher than in patients without T2DM (9.8% vs. 6.0%, $P < 0.001$) (Fig. 3). In patients with T2DM, the event rate was lower in the intensive group, 10.3% vs. 9.4%, but this difference was nonsignificant ($P = 0.32$). The event rate in patients without T2DM was also lower in the intensive group: 6.8% vs. 5.2% ($P < 0.001$). The interaction between the intervention and T2DM was nonsignificant when an interaction term was added to the Cox

Table 1—Baseline characteristics of ACCORD-BP and SPRINT and the baseline characteristics of the pooled cohort per randomization arm

	Baseline by study		Baseline by randomization		
	ACCORD-BP	SPRINT	Standard	Intensive	*P*
N	4,733	9,361	7,054	7,040	
Age, years	62.7 (6.7)	67.9 (9.4)	66.2 (9.0)	66.2 (8.9)	0.99
Female, *n* (%)	2,258 (47.7)	3,332 (35.6)	2,778 (39.4)	2,812 (39.9)	0.51
Race or ethnic group, *n* (%)					0.585
Non-Hispanic black	1,127 (23.8)	2,802 (29.9)	2,003 (28.4)	1,926 (27.4)	
Hispanic	330 (7.0)	984 (10.5)	651 (9.2)	663 (9.4)	
Other	495 (10.5)	176 (1.9)	331 (4.7)	340 (4.8)	
Non-Hispanic white	2,781 (58.8)	5,399 (57.7)	4,069 (57.7)	4,111 (58.4)	
SBP, mmHg	1,39.2 (15.8)	139.7 (15.6)	139.56 (15.4)	139.46 (15.9)	0.71
Diastolic blood pressure, mmHg	76.0 (10.4)	78.1 (11.9)	77.35 (11.5)	77.45 (11.5)	0.60
History of CVD, *n* (%)	1,593 (33.7)	1,877 (20.1)	1,726 (24.5)	1,744 (24.8)	0.69
Framingham 10-year cardiovascular death risk in %*	32 (22, 45)	22 (15, 32)	25 (17, 36)	25 (17, 37)	0.64
Nonsmoker, *n* (%)	4,107 (86.8)	8,121 (86.8)	6,141 (87.1)	6,087 (86.5)	0.31
BMI	32.2 (5.5)	29.9 (5.8)	30.58 (5.7)	30.67 (5.9)	0.33
Serum creatinine, mg/dL	0.9 (0.2)	1.1 (0.3)	1.0 (0.3)	1.0 (0.3)	0.78
Estimated GFR, mL/min/1.73 m^2	91.6 (28.8)	71.7 (20.6)	78.4 (24.8)	78.4 (26.1)	0.99
Ratio of urinary albumin (mg) to creatinine (g)	15.0 (7.0, 47.0)	9.5 (5.6, 21.4)	10.8 (6.0, 28.2)	11.0 (6.0, 28.0)	0.46
Total cholesterol, mg/dL	192.8 (44.7)	190.1 (41.2)	190.5 (42.1)	191.5 (42.7)	0.16
HDL, mg/dL	46.3 (13.7)	52.9 (14.5)	50.7 (14.7)	50.6 (14.3)	0.93
Plasma triglycerides, mg/dL	147.0 (98.0, 226.0)	107.0 (77.0, 150.0)	117.0 (82.0, 172.0)	117.0 (82.0, 173.0)	0.72
Aspirin use, *n* (%)	2,473 (52.5)	4,756 (51.0)	3,559 (50.7)	3,670 (52.3)	0.05
Statin use, *n* (%)	3,065 (65.0)	4,054 (43.7)	3,632 (51.9)	3,487 (49.8)	0.02
T2DM, *n* (%)	4,733 (100.0)	0 (0.0)	2,371 (33.6)	2,362 (33.6)	0.95

Data are mean (SD) or median (interquartile range) unless otherwise specified. GFR, glomerular filtration rate. *Only for patients without a history of CVD (*n* = 10,624).

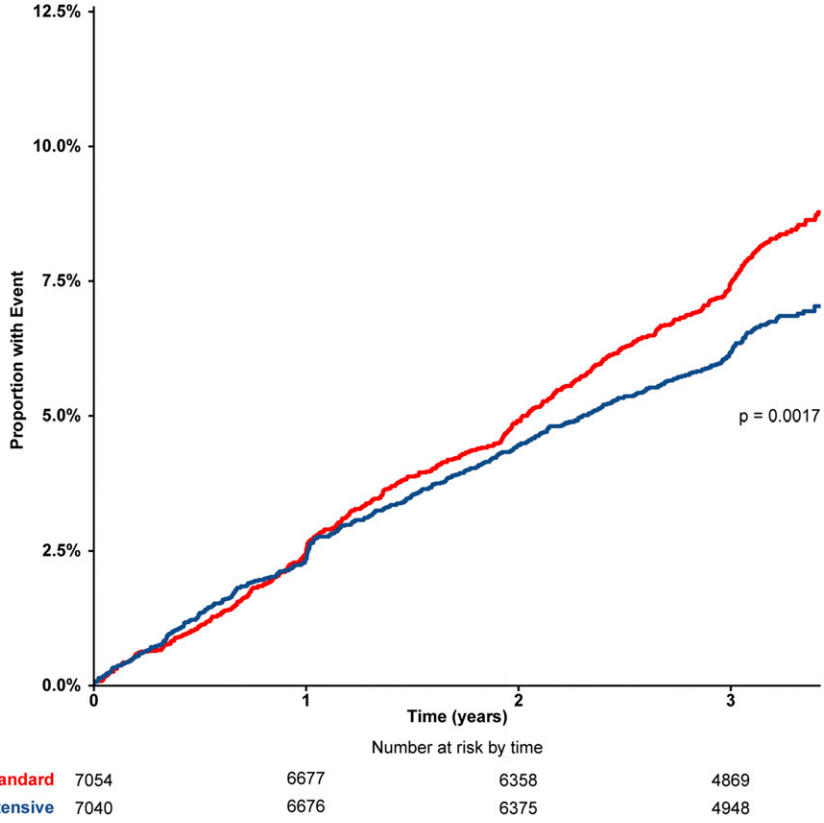


Figure 1—A Kaplan-Meier plot of the composite primary end point in the pooled cohort (n = 14,094). Primary composite end point consists of myocardial infarction, stroke, and cardiovascular death plus unstable angina and acute cardiac decompensation. The hazard ratio for primary end point event is 0.82 (95% CI 0.73–0.93), P = 0.0017. No significant interaction between T2DM and treatment allocation was observed (P for interaction = 0.13).

model (P = 0.13). Also, the model fit did not improve when an interaction term was forced in the Cox model (AIC 19,205 vs. 19,205, P = 0.13), indicating that there is no evidence that intensive blood pressure lowering to 120 mmHg has a different relative effect in patients with T2DM compared with patients without T2DM. The post hoc calculated power in ACCORD-BP using the SPRINT composite end point was 17.5% vs. 91.6% in SPRINT at 3.26 years median follow-up duration. With the observed treatment effect in ACCORD-BP, ~50,000 patients would be needed to reach 90% power.

Cardiovascular Risk

In patients without a history of cardiovascular events, those with T2DM had a significantly higher calculated baseline risk of CVD compared with those without T2DM (median 32% vs. 22%, $P < 0.001$). The baseline risk scores were stratified per 20% increment in 10-year risk (Supplementary Fig. 5). None of the subgroups for risk had a significant interaction with treatment allocation. Also, the model fit did not improve when an interaction term was forced in the Cox model (AIC 10,243 vs. 10,248, P = 0.84). This indicates that there is no evidence that the relative treatment effect of intensive blood pressure lowering depends on the 10-year risk of CVD. In the subgroup of patients with a history of CVD (n = 3,470), intensive treatment resulted in a nonsignificant reduction of the primary end point (13.8% vs. 12.5%, P = 0.29).

Safety Events

Serious adverse events related to blood pressure–lowering therapy occurred more often in the intervention group (6.5% vs. 4.6%, $P < 0.001$). The interaction between T2DM and intensive blood pressure lowering for safety events could not be investigated, as these data were not publicly available for all patients.

CONCLUSIONS

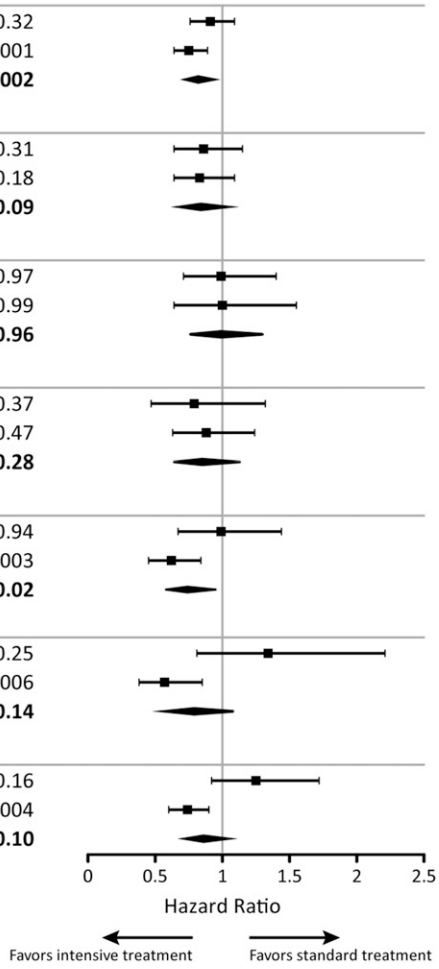
Our study suggests that there is no difference in the relative treatment effect of intensive blood pressure lowering in patients with and patients without T2DM at increased risk of CVD and with an SBP between 130 mmHg and 180 mmHg. Second, when the broader SPRINT composite primary end point that additionally included unstable angina and heart failure is applied to ACCORD-BP, the primary end point remains nonsignificantly in favor of intensive blood pressure lowering. Third, there is no evidence for the presence of an interaction between baseline risk of CVD as calculated with the Framingham risk score in primary prevention patients and the relative treatment effect of intensive blood pressure lowering on the primary end point.

In the current analysis, we sought to eliminate the effect of difference in study design by harmonizing the composite primary end point and the follow-up duration in the two studies. The main outcomes of ACCORD-BP remained unchanged when the end point and follow-up duration of SPRINT were applied. The post hoc calculated power in ACCORD was low owing to the smaller relative risk reduction and sample size.

By combining the data sets of two studies that applied the same intervention for the same indication to patients with and patients without T2DM, we were able to investigate whether an interaction exists between intensive blood pressure lowering and T2DM. In this analysis, there was no evidence for such an interaction. This implies that the primary outcome of the pooled cohort (hazard ratio 0.82 [95% CI 0.73–0.93]) should not be interpreted differently for patients with T2DM and patients without T2DM (Fig. 2). The presence of T2DM may be a marker of increased baseline risk of CVD, which in turn could affect the relative treatment effect of intensive blood pressure lowering. Therefore, the presence of an interaction between 10-year risk score in patients without a history of CVD and intensive blood pressure lowering was assessed, but no significant interaction was found.

Several analyses have addressed the question of whether the effect of intensive blood pressure lowering is different in patients with versus patients without T2DM (14–16). These analyses did not have access to individual patient data. Therefore, overall treatment effects could not be pooled and differences in baseline characteristics, outcomes, and follow-up duration could not be taken

N (pooled) *Primary end point*	Intensive N= 7040 Events (%)	Standard N = 7054 Events (%)	HR	95% CI low	95% CI high	P
T2DM	222 (9.4)	244 (10.3)	0.91	0.76	1.09	0.32
No T2DM	243 (5.2)	319 (6.8)	0.75	0.64	0.89	<0.001
Pooled	**465 (6.6)**	**563 (8.0)**	**0.82**	**0.73**	**0.93**	**0.002**
Myocardial infarction						
T2DM	83 (3.5)	97 (4.1)	0.86	0.64	1.15	0.31
No T2DM	97 (2.1)	116 (2.5)	0.83	0.64	1.09	0.18
Pooled	**180 (2.6)**	**213 (3.0)**	**0.84**	**0.69**	**1.03**	**0.09**
Unstable angina						
T2DM	65 (2.8)	66 (2.8	0.99	0.71	1.40	0.97
No T2DM	40 (0.9)	40 (0.9)	1.00	0.64	1.55	0.99
Pooled	**105 (1.5)**	**106 (1.5)**	**0.99**	**0.76**	**1.3**	**0.96**
Stroke						
T2DM	26 (1.1)	32 (1.3)	0.79	0.47	1.32	0.37
No T2DM	62 (1.3)	70 (1.5)	0.88	0.63	1.24	0.47
Pooled	**88 (1.2)**	**102 (1.4)**	**0.85**	**0.64**	**1.13**	**0.28**
Heart failure						
T2DM	52 (2.2)	53 (2.2)	0.99	0.67	1.44	0.94
No T2DM	62 (1.3)	100 (2.1)	0.62	0.45	0.84	0.003
Pooled	**114 (1.6)**	**153 (2.2)**	**0.74**	**0.58**	**0.95**	**0.02**
Cardiovascular death						
T2DM	35 (1.5)	27 (1.1)	1.34	0.81	2.21	0.25
No T2DM	37 (0.8)	65 (1.4)	0.57	0.38	0.85	0.006
Pooled	**72 (1.0)**	**92 (1.3)**	**0.79**	**0.58**	**1.08**	**0.14**
All–cause death						
T2DM	87 (3.7)	70 (3.0)	1.25	0.92	1.72	0.16
No T2DM	155 (3.3)	210 (4.5)	0.74	0.60	0.90	0.004
Pooled	**242 (3.6)**	**280 (4.0)**	**0.86**	**0.73**	**1.03**	**0.10**



T2DM (intensive): N = 2362
T2DM (standard): N = 2371
No T2DM (intensive): N = 4678
No T2DM (standard): N = 4683

Figure 2—Composite primary and individual secondary end points. T2DM represents the ACCORD-BP subgroup for which follow-up was truncated at the median follow-up of the SPRINT trial (3.26 years). "No T2DM" represents the SPRINT subgroup. The composite primary end point of SPRINT was used and consists of unstable angina, myocardial infarction, acute cardiac decompensation, stroke, and cardiovascular death.

into account. A recent meta-analysis that examined differences in outcomes in patients with and without T2DM according to attained blood pressure levels concluded that, in contrast to patients without T2DM, there is little or no further benefit in lowering SBP below 130 mmHg. Our analysis is the first to pool individual patient data from the only two randomized clinical trials that assessed the effect of targeting an SBP <120 mmHg vs. <140 mmHg. After harmonization of the composite primary end point and the follow-up duration, we were able to calculate the treatment effect on the same end point over the same follow-up duration. The individual patient data provide a more precise estimate of the treatment effect. We show that, in contrast to the divergent benefit below an SBP level of 130 mmHg in a recent meta-analysis (16), the benefit of lowering blood pressure targeted at an SBP <120 mmHg is not different in patients with and without T2DM. In addition, this analysis allowed us to answer the question of whether baseline cardiovascular risk (expressed as the 10-year risk of CVD) is an effect modifier of the benefit of intensive blood pressure lowering, as patients with T2DM have a higher 10-year cardiovascular risk compared with those without. We did not find such a modifying effect caused by baseline cardiovascular risk.

Observational data have suggested that aggressive blood pressure lowering may increase cardiovascular events, indicating the potential presence of a "J-curve" phenomenon in some high-risk patients. However, in this pooled cohort, patients were experimentally exposed to different blood pressure targets and care providers were not restricted to specific blood pressure–lowering drugs. Possibly, the increase of harm in trials such as the ROADMAP study (Randomized Olmesartan and Diabetes Microalbuminuria Prevention), ALTITUDE (Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints [Core and Extension Phases]), and ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial) may be due to double renin-angiotensin system blockade instead of intensive blood pressure lowering (17–19).

Clinical Implications

The latest guidelines from the American Heart Association, the American Diabetes

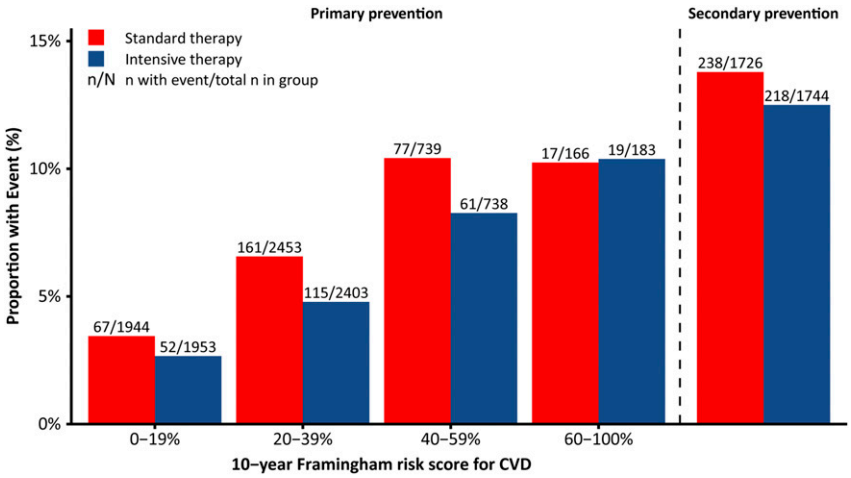


Figure 3—Percentage of patients with a primary end point event for Framingham 10-year CVD risk score in primary prevention patients and in all secondary prevention patients. No significant interaction between 10-year risk score and treatment allocation was observed in the primary prevention subgroup (P for interaction = 0.64).

Association, and the European Society of Cardiology recommend an SBP target of <140 mmHg in patients with T2DM, while <130 mmHg may be appropriate for certain individuals, such as younger patients (6–8). The results of SPRINT have not been incorporated in these guidelines, as the results were published recently. We found that based on the available data, there is no evidence that T2DM patients do not benefit from intensive blood pressure lowering. The reduction of the primary end point and the increase in serious adverse events related to intensive blood pressure lowering is similar. Therefore, tailoring the treatment for the individual patient seems appropriate based on the goals of the individual patient, life expectancy, and the likelihood of the adverse events to occur.

Limitations

This study is a post hoc analysis, in which the results of two independent, randomized, open-label studies are pooled and the end points harmonized. Pooling of the studies was deemed appropriate based on both clinical and methodological grounds, with the inclusion and exclusion criteria of both studies and the study intervention taken into account. The null hypothesis was that the treatment effect is not different in patients with T2DM or with a higher 10-year risk score. This hypothesis was not rejected in this analysis, and the results should be interpreted as such. Therefore, this analysis does not exclude a difference in the treatment effect of intensive blood pressure lowering between patients with T2DM and patients without T2DM. It is important to note that in ACCORD-BP an observer was present during blood pressure measurements, whereas in SPRINT no observer was present (20). The direction of bias is that SPRINT patients may have had slightly higher blood pressures when at home compared with those who participated in ACCORD-BP, as patients in ACCORD-BP were subject to the white coat effect (21). However, the absolute difference in blood pressure in both trials was of the same magnitude.

The most important limitation of this analysis is that the serious adverse event data were not available at patient level in the ACCORD-BP public data set. As a result of this, we were not able to assess the interaction between serious adverse events related to intensive blood pressure–lowering therapy and T2DM. However, it is clear that intensive blood pressure lowering results in more serious adverse events both in patients with T2DM and in patients without T2DM. Therefore, it is important to weigh the potential benefit and harm of intensive blood pressure lowering for the individual patient (22).

Conclusion

In this pooled cohort, intensive blood pressure lowering to an SBP target <120 mmHg reduces the cardiovascular events in patients with an increased cardiovascular risk and an SBP between 130 mmHg and 180 mmHg. Cardiovascular mortality and all-cause mortality were not significantly different. These analyses do not provide any evidence for a differential effect of intensive blood pressure lowering in patients with T2DM or a higher 10-year risk of CVD.

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Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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References

1. Stamler J, Neaton JD, Wentworth DN. Blood pressure (systolic and diastolic) and risk of fatal coronary heart disease. Hypertension 1989;13 (Suppl. 5):2–12
2. Huxley R, Barzi F, Woodward M. Excess risk of fatal coronary heart disease associated with diabetes in men and women: meta-analysis of 37 prospective cohort studies. BMJ 2006;332:73–78
3. Kearney PM, Whelton M, Reynolds K, Muntner P, Whelton PK, He J. Global burden of hypertension: analysis of worldwide data. Lancet 2005; 365:217–223
4. Cushman WC, Evans GW, Byington RP, et al.; ACCORD Study Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med 2010;362:1575–1585
5. Wright JT Jr, Williamson JD, Whelton PK, et al.; SPRINT Research Group. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med 2015;373:2103–2116
6. Rosendorff C, Lackland DT, Allison M, et al.; American Heart Association, American College of Cardiology, and American Society of Hypertension. Treatment of hypertension in patients with coronary artery disease: a scientific statement from the American Heart Association, American College of Cardiology, and American Society of Hypertension. Hypertension 2015;65:1372–1407
7. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J 2013;34:2159–2219
8. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013;36(Suppl. 1):S11–S66
9. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the

panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA 2014;311:507–520
10. Ambrosius WT, Sink KM, Foy CG, et al.; SPRINT Study Research Group. The design and rationale of a multicenter clinical trial comparing two strategies for control of systolic blood pressure: the Systolic Blood Pressure Intervention Trial (SPRINT). Clin Trials 2014;11:532–546
11. Cushman WC, Grimm RH Jr, Cutler JA, et al.; ACCORD Study Group. Rationale and design for the blood pressure intervention of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Am J Cardiol 2007;99(Suppl.):S44–S55
12. D'Agostino RB Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–753
13. R Core Team. *R: A Language and Environment for Statistical Computing*. Vienna, Austria, R Foundation for Statistical Computing, 2015
14. Perkovic V, Rodgers A. Redefining blood-pressure targets–SPRINT starts the marathon. N Engl J Med 2015;373:2175–2178
15. Malhotra R, Nguyen HA, Benavente O, et al. Association between more intensive vs less intensive blood pressure lowering and risk of mortality in chronic kidney disease stages 3 to 5: a systematic review and meta-analysis. JAMA Intern Med 2017;177:1498–1505
16. Thomopoulos C, Parati G, Zanchetti A. Effects of blood-pressure-lowering treatment on outcome incidence in hypertension: 10 - Should blood pressure management differ in hypertensive patients with and without diabetes mellitus? Overview and meta-analyses of randomized trials. J Hypertens 2017;35:922–944
17. Haller H, Ito S, Izzo JL Jr, et al.; ROADMAP Trial Investigators. Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;364:907–917
18. Parving H-H, Brenner BM, McMurray JJV, et al.; ALTITUDE Investigators. Cardiorenal end points in a trial of aliskiren for type 2 diabetes. N Engl J Med 2012;367:2204–2213
19. ONTARGET Investigators, Yusuf S, Teo KK, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. N Engl J Med 2008;358:1547–1559
20. Kjeldsen SE, Lund-Johansen P, Nilsson PM, Mancia G. Unattended blood pressure measurements in the systolic blood pressure intervention trial: implications for entry and achieved blood pressure values compared with other trials. Hypertension 2016;67:808–812
21. Myers MG, Godwin M, Dawes M, et al. Conventional versus automated measurement of blood pressure in primary care patients with systolic hypertension: randomised parallel design controlled trial. BMJ 2011;342:d286
22. de Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284